Soluble adhesion molecules in immune mediated liver disease

The migration of circulating neutrophils, monocytes, and lymphocytes into perivascular tissues entails the interaction of specific ligands on their surface with receptors on endothelial cells. These ligands and their receptors have been defined as 'adhesion molecules' in vitro studies have shown that cellular expression of these molecules is affected by cytokines, for example, interleukin 1 (IL 1), tumour necrosis factor alpha (TNF α), and interferon gamma (IFN γ). Immunohistochemistry studies have shown that increased tissue expression occurs in inflamed tissue, including liver tissue from patients with hepatitis. Cytokines of the chemokine family such as MIP-1β can also enhance adhesion by increasing the affinity of the leucocyte ligands for particular adhesion molecules expressed on the endothelial cell membrane. Soluble forms of several adhesion molecules have recently been identified in serum and plasma whose measurement may permit ready monitoring of inflammatory diseases or immunotherapy and improve our understanding of the immunopathogenesis of disease.

Adhesion molecules

Adhesion molecules can be classified into three main groups according to their structure: (a) the immunoglobulin supergene family (intercellular adhesion molecule 1 (ICAM 1) and vascular cell adhesion molecule 1 (VCAM 1)); (b) the integrin family (composed of non-covalently linked variable α and β chain heterodimers LFA-1 and Mac-1, the ligands for ICAM-1); and (c) the selectins (so called because of the terminal lectin like domain, for example, P selectin, E selectin, and L selectin). Most clinical studies of soluble adhesion molecules have concentrated on ICAM 1. This review considers both ICAM 1 and VCAM 1, E-selectin, and P-selectin for which some data are available.

ICAM 1 is a 85–110 kD glycoprotein of five tandemly arranged immunoglobulin like domains. It is constitutively expressed on a few cell types, but after stimulation with IL 1, TNF α, or IFN γ, expression is induced on a wide variety of cells including lymphocytes, endothelial cells, fibroblasts, biliary epithelial cells, and hepatocytes. In vitro studies have shown that the degree and the time course of induction of ICAM 1 by cytokines is dependent on the particular cell type. Interaction between endothelial cell ICAM 1 and its integral ligands, lymphocyte function activation antigen 1 (LFA 1) and Mac 1 expressed on circulating neutrophils, monocytes, and lymphocytes is important in the migration of these cells from the circulation into the tissues. ICAM 1 participates in the interaction between T cells and antigen presenting cells including other T cells and B cells. It is also a receptor for rhinoviruses and Plasmodium falciparum infected erythrocytes. In the rare genetic defect, leucocyte adhesion deficiency, there is an abnormality of the integrin ligands for ICAM 1. This results in defective neutrophil migration onto sites of inflammation associated with increased risk of infection although lymphocyte extravasation remains normal.

Circulating soluble forms of ICAM 1 (sICAM 1) were first identified in serum samples in controls and patients with inflammatory diseases using blotting and enzyme linked immunosorbent assay (ELISA) techniques. sICAM 1 in serum has a similar molecular weight to recombinant sICAM 1 and retains the capacity to bind to its integrin ligand, LFA 1. Cytokine activated human umbilical vein endothelial cells, cultured peripheral blood mononuclear cells, and B lymphoblastoid cell lines all secrete sICAM 1 in vitro without cell necrosis. sICAM 1 results from proteolytic cleavage of membrane bound ICAM 1 close to the cell membrane, but increased cell expression of ICAM 1 is not necessarily followed by release of sICAM 1. The cellular source of sICAM 1 in vivo remains to be determined. The function of sICAM 1 is unknown; it may function to break adhesion, as an adhesion blocker, to induced transmembrane signalling by LFA 1 or as an anti-kinoviral agent.

VCAM 1 (also known as INCAM 110) is a 110 kD glycoprotein of seven tandemly arranged immunoglobulin like domains. An alternative spliced variant consisting of six immunoglobulin like domains has also been identified in activated vascular endothelium. VCAM 1 expression is more limited than ICAM 1, but may be induced in several cell lineages by cytokines and like ICAM 1 the time course and degree of induction is dependent on the cell type studied. The interaction between VCAM 1 and its integrin ligand, very late activation antigen 4 (VLA 4), is important in the adhesion of monocytes, lymphocytes, and eosinophils with activated endothelium. VCAM 1 can also mediate B cell adhesion to dendritic cells and melanoma cell adhesion to endothelium and so may participate in melanoma metastases.

Soluble VCAM 1 (sVCAM 1), like sICAM 1, is released from cytokine activated cultured human umbilical vein endothelial cells probably by proteolytic cleavage at or near the cellular membrane without cell necrosis occurring. ELISA techniques have identified sVCAM 1 in the serum of controls and patients with inflammatory disease. The functions of sVCAM 1 is unknown, but are probably similar to those of sICAM 1.

E selectin is a 115 kD glycoprotein, formally known as endothelial leucocyte adhesion molecule 1 (ELAM 1) or LECAM 2, consisting of a N-terminal lectin like domain, an epidermal growth factor like domain, and a region of six consensus repeats of a domain found in complement binding proteins. E selectin is only expressed on cytokine stimulated vascular endothelium. In vitro, stimulation of human umbilical vein endothelial cells with TNF α is followed by peak expression after four hours, which declines to basal values after 24 hours. E selectin mediates adherence of neutrophils, monocytes, and a subpopulation of memory T cells to activated endothelium and binding also induces the activation of leucocyte integrins, such as Mac 1. The ligands for E selectin include the sialyl Lewisα antigen, Lewisα antigen, and related fucosylated N-acetyl-lactosamines, which are expressed on circulating white cells and also on some tumour cells.

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Soluble E selectin (sE selectin) is released in low concentrations from human umbilical vein endothelial cells stimulated with TNF α and IL 1 by a mechanism thought to involve proteolysis at or near the cell membrane. Using ELISA techniques sE selectin has been identified in serum from controls and patients with diabetes or renal failure. sE selectin may function as a chemoattractant and can also activate leukocyte integrin ligands.

P selectin, previously known as granule membrane protein 140 (GMP 140), CD62 or platelet activation dependent granule external membrane protein (PADGEM) is a 140 kD glycoprotein with nine consensus repeats of complement binding protein domains. P selectin is localised within the α granules of platelets and Weibel-Palade bodies of endothelial cells. After stimulation of these cells with thrombin, histamine, or leukotrienes, P selectin is translocated to the cell surface within minutes. The ligands for P selectin are the same as E selectin, and thus P selectin acts to mediate the adhesion of neutrophils and monocytes to activated platelets and endothelial cells.

In contrast with the other soluble adhesion molecules, described thus far, soluble P selectin (sP selectin) is produced by alternative splicing of the mRNA, which results in an inframe deletion of 40 amino acids that encode for the transmembrane domain. The function of sP selectin in vivo is unknown.

**Adhesion molecules in liver disease**

**Normal liver**

Immunohistochemical studies have shown that ICAM 1 expression is restricted to the sinusoidal lining cells and endothelial cells lining sinusoids and portal vessels. Hepatocytes are either negative or have faint membranous staining for ICAM 1 and biliary epithelium is mainly negative. E selectin, P selectin or VCAM 1 expression is not seen. All studies using ELISA techniques have identified low expressions of sICAM 1, sVCAM 1, sP selectin, and E selectin in apparently normal controls.

**Hepatitis**

Immunohistochemical studies have shown increased ICAM 1 expression on hepatocytes in patients with hepatitis, the pattern of staining is dependent on the aetiology of the inflammation. Increased ICAM 1 and E selectin expression occurs on hepatic sinusoidal lining cells throughout the liver in acute hepatitis. Weak E selectin expression is limited to the sinusoidal lining cells in intralobular and perportal areas of inflammation in chronic active hepatitis. Sinusoidal lining cells in areas of perportal and intralobular inflammation strongly express VCAM 1 in chronic active hepatitis with only weak staining occurring in acute hepatitis.

sICAM 1 expression is significantly increased in patients with acute viral and drug induced hepatitis, chronic active hepatitis, and active cirrhosis. Treatment of patients with autoimmune chronic active hepatitis with corticosteroids reduces sICAM 1 expression, although values may remain increased in patients with cirrhosis. Patients with autoimmune chronic active hepatitis also have significantly increased expression of sE selectin and sVCAM 1, which also fall with corticosteroid treatment. Patients with hepatitis C related chronic active hepatitis have high expression of sICAM 1, the values of sICAM 1 fall if the patients respond to interferon treatment.

**Primary biliary cirrhosis and primary sclerosing cholangitis**

In immunohistochemical studies, ICAM 1 expression is increased on interlobular bile ducts, proliferating ductules, and periseptal hepatocytes in patients with primary biliary cirrhosis and primary sclerosing cholangitis. Medium sized bile ducts are uniformly negative for ICAM 1 and endothelial lining cells have similar staining to controls.

Expression of sICAM 1, sVCAM 1, and sE selectin is increased in patients with primary biliary cirrhosis and primary sclerosing cholangitis. sICAM 1 expressions increase with progression of primary biliary cirrhosis but treatment with methotrexate has no effect on the expression of these adhesion molecules. The effect of other forms of treatment, including ursodeoxycholic acid is unknown.

**Inactive cirrhosis**

Immunohistochemical staining for E selectin and VCAM 1 is infrequent and focal, around small areas of periseptal inflammation. However, periseptal hepatocyte staining for ICAM 1 is a more common finding in cirrhosis.

Increased expressions of sICAM 1 persist in patients with chronic active hepatitis treated with corticosteroids only if cirrhosis is present. This poses the question as to whether or not the sICAM 1 is produced from the liver during inflammation or is simply increased because of failure of the liver to clear sICAM 1 as a consequence of portasystemic shunting.

**Transplantation**

A comprehensive immunohistochemical study of adhesion molecule expression after liver transplantation, including graft rejection, has recently been described. Increased expression of ICAM 1, VCAM 1, P selectin, and E selectin occurs on endothelial cells in acute and chronic rejection and during infective complications. These complications of transplantation are also associated with increased expression of ICAM-1 on hepatocytes. After immunosuppressive treatment for acute rejection, ICAM 1 staining within the liver is reduced.

sICAM 1, sE selectin, and sVCAM 1 are increased after liver transplantation (Simpson et al, unpublished data). sICAM 1 is probably produced within the liver graft during acute rejection as it is also found in bile. Increased sICAM 1 expressions in bile and blood may precede the detection of clinically apparent acute rejection, sICAM 1 expressions fall after successful corticosteroid treatment. Infection and other non-rejection complications of transplantation are also associated with increased sICAM 1, but biliary values are unchanged.

**Conclusion**

Adhesion molecule expression is fundamentally important in inflammation and autoimmunity. Our knowledge of their role in the pathogenesis of immune mediated liver disease has been developed by careful immunohistochemical study. The identification of soluble forms of many of these molecules provides the potential for further clinical study of their role in the monitoring of inflammatory disease affecting the liver and the use of immunomodulatory treatment and may also improve our understanding of the immunopathogenesis of these diseases.


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